IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:

Jacques DUMAS et al.		Confirmation No.:	8474
Serial No.:	09/472,232	Examiner:	Deepak Rao
Filed:	December 27, 1999	Group Art Unit:	1624
Title:	INHIBITION OF RAF KINASE USING ARYL AND HETEROARYL SUBSTITUTED HETEROCYCLIC UREAS		

BRIEF ON APPEAL

Mail Stop Appeal Brief-Patents
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

Further to the Notice of Appeal filed on October 11, 2005, please consider the following.

The attached check includes the fee of $500.00 as set forth under § 41.20(b)(2) and the fee of $1020 for a three-month extension of the period to respond . The Commissioner is hereby authorized to charge any fees associated with this response or credit any overpayment to Deposit Account No. 13-3402.

(i) REAL PARTY IN INTEREST

The real party in interest is: BAYER PHARMACEUTICALS CORPORATION, 400 Morgan Lane, West Haven, Connecticut 06516, United States of America, a corporation organized under the laws of the State of Delaware, United States of America.

(ii) RELATED APPEALS AND INTERFERENCES

Another application, Serial No. 09/776,936, filed December 22, 1998, assigned to Bayer Pharmaceuticals Corporation, is on appeal. This application also contains claims to methods that are rejected under 35 USC § 112, first paragraph, as allegedly non-enabled. These method claims employ distinct urea compounds for the treatment of a cancerous cell

growth mediated by raf kinase, including the treatment of lung carcinoma, pancreas carcinoma, thyroid carcinoma, bladder carcinoma, colon carcinoma and myeloid leukemia.

(iii) STATUS OF CLAIMS

Claims 1, 2, 4-6, 9, 10, 15, 16, 18-34 and 38-40 are pending in the present application

Claims 25, 32-34 and 39 are allowed.

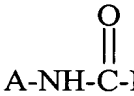
Claims 1, 2, 4-6, 9, 10, 15, 16, 18-24, 26-31, 38 and 40 are rejected. All rejected claims are on appeal and appear in the attached Appendix.

(iv) STATUS OF AMENDMENTS

No amendments were filed or proposed after the final rejection.

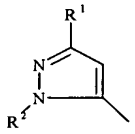
(v) SUMMARY OF CLAIMED SUBJECT MATTER

Appellants' invention is directed to aryl urea compounds according to formula I below which inhibit the raf pathway



I

In formula I, A is:



B is a cyclic moiety substituted by –M-L^1, R^1 is a linear or cyclic alkyl group and R^2 is an aryl or heteroaryl group, (see page 2, lines 22-28 and page 7, lines 4-11 and claims 1-2, 4, 5, 6, 7, 8, 9, 10-14, 30-31,40) These moieties are further defined in the claims and on pages 2-9 of the specification.

The invention also relates to pharmaceutical compositions, which contain the compounds of formula, I (see page 14, lines 1-2 and claims 24 and 25).

The invention further relates to methods for the treatment of tumors and/or cancerous cell growth mediated by the enzyme raf kinase. These methods comprise administering a compound of formula I, (see page 2, lines 6-10 and claims 15-16, 18-23, 26-29 and 38). The methods of this invention include the treatment of a solid cancers (tumors), carcinomas such as carcinomas of the lung, pancreas, thyroid, bladder or colon, myeloid disorders such as myeloid leukemia and adenomas such as villous colon adenomas or adenomas (see page 2, lines 14-17 and claims 26-29 and 38).

(vi) GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

The grounds for rejections are:

(1) the rejection under 35 U.S.C. § 112, first paragraph, i.e., whether claims 15-16, 18-23, 26-29 and 38 directed to methods for the treatment of a cancerous cell growth mediated by raf kinase (including specific carcinomas named in claims 26-29) by compounds of formulae I, are enabled, and

(2) the rejection under 35 U.S.C. § 103, i.e., whether claims 1, 2, 4-6, 9-10, 15, 16, 18-24, 26-31, 38 and 40, directed to compounds of formula I, are unpatentable over Regan et al., U.S. Patent No. 6,080,763.

(vii) ARGUMENT

The Rejection Under 35 USC § 112

Method claims 15–16 and 18–23 are directed to treating diseases "mediated by raf kinase" using the compounds of formula I. The functional definition used to define the diseases is commensurate in scope with the raf kinase activity of the compounds of formula I, which is demonstrated by the results (IC_{50} values) of the raf kinase assays disclosed in the specification on page 34.

Method claims 26–29 and 38 define methods for treating a tumor, solid cancer, melanoma or adenoma with a compound of formula I. The specification cites a number of publications (Monia et al., Kolch et al, Daum et al. and Fridman et al) on pages 1 and 2, which are representative of the state of the art at the time of the invention. These publications demonstrate the inhibition of raf kinase was correlated with the inhibition of the growth of a variety of tumor types at the time of the invention. Treatment approaches

dependent on the inhibition of raf signaling were developed by the mid-late 1990's and a number of research groups disclosed assays for measuring the ability of compounds to inhibit raf activity, consistent with the present application. See for example WO 97/36587, Heimbrook et al.

No evidence has been presented to refute the disclosures and conclusions made in these publications and no evidence has been presented which raises any doubt as to the asserted utility of the compounds of formula I.

The examiner alleges,

> None of the state of the art references of record expressed a single therapeutic approach for treating all types of diseases mediated by RAF kinase or cancerous cell growth generally by administering a single class of compounds.

In response, reference is made to disclosures within WO 97/36587 and WO 98/22103. WO 98/22103 describes the broad utility of raf kinase inhibitors in citing six references on pages 1 and 2, which are said to provide "evidence that inhibitors of raf will result in anti-tumor activity," and taken together these references indicate that:

> raf is both a direct and major effector of ras function and as such inhibition of the kinase activity of raf is expected to have antitumour activity in at least a proportion of human tumors.
>
> Specific cancers of interest include:
>
> carcinoma, including that of the bladder, breast, colon, kidney, liver, lung, ovary, pancreas, stomach, cervix, thyroid, and skin;
>
> hematopoietic tumors of lymphoid lineage, including lymphocytic leukemia, B-cell lymphoma, and Burketts lymphoma;
>
> tumors of mesenchymal origin, including fibersarcoma and rhabdomya sarcoma; and other tumors, including melanoma, seminoma, tetratocarcinoma; neuroblastoma and glioma. (Emphasis added.)

WO 97/36587 states on page 1,

> Since inhibition of growth in soft agar is highly predictive of tumor responsiveness in whole animals, these studies suggest that the antagonism of Raf is an effective means by which to treat cancers in which Raf plays a role. Examples of cancers where Raf is implicated through over expression include cancers of the brain, genitourinary tract, lymphatic system, stomach, larynx, and lung.

In addition, applicants note that Monia et al. state in their abstract,

> These studies strongly suggest that antisense inhibitors targeted against the C-raf-1 kinase may be of considerable value as antineoplastic agents that display activity against a wide spectrum of tumor types at well tolerated doses.

Furthermore, Fridman et al., another reference cited in the specification, states,

> Such a drug (a specific anti-Ras chemical drug) would be potentially useful for the treatment of Ras-associated cancers, which represent about 30% of total human carcinomas, notably more than 90% of pancreas carcinomas and 50% of colon carcinomas.

These disclosures demonstrate the state of the art was not limiting with respect to the types of cancerous cell growth treated where raf plays a role.

The specification provides ample guidance as to how to prepare the compounds of formula I in the general methods on pages 10-13 and specific methods on pages 17-33. The specification also provides ample guidance in preparing pharmaceutical compositions with the compounds of this invention (pages 14-16) and how to administer these compositions in the treatment of cancers. See, e.g., pages 10-14. The specification also provides dosage ranges for the various methods of administration (see page 16-17). Given the extent of the disclosure provided, it would at most involve routine experimentation, if any at all, for one of ordinary skill in the art to treat any one of the diseases mediated by raf kinase of claims 15–16 and 18–23 or the specific cancers of claims 26–29 and 38 with a compound of this invention.

Additionally, "the [enablement] requirement is satisfied if, given what they [, those of ordinary skill in the art,] already know, the specification teaches those in the art enough that they can make and use the claimed invention without 'undue experimentation.'" See *Amgen v Hoechst Marion Roussel*, 314 F.2d 1313, 65 USPQ2d 1385 (Fed. Cir. 2003). Using the claimed compounds would be routine for those of ordinary skill in the art in view of applicant's disclosure. "An inventor need not ... explain every detail since he is speaking to those skilled in the art," *In re Howarth,* 654 F.2d105, 210 U.S.P.Q. 689 (CCPA 1981). "Not every last detail is to be described, else patent specifications would turn into production specifications, which they were never intended to be." *In re Gay*, 309 F.2d 769, 774, 135 U.S.P.Q 311 (CCPA 1962).

The specification clearly provides sufficient disclosure to satisfy the requirements of 35 USC §112 for claims 15-19 and 28-33. In rejecting these claims the Examiner is requiring that the application meet clinical standards as set by the FDA to satisfy the enablement requirement under 35 U.S.C. § 112, first paragraph, in making the following observations:

> Rigorously planned and executed clinical trials, incorporating measurement of appropriate biomarkers and pharmacodynamic end points are critical for electing the optimal dose and schedule. A detailed understanding of the molecular mode of action of RAF kinase inhibitors alongside the elucidation of the molecular pathology of individual cancers is required to identify tumor types and individual patients that may benefit most from treatment. It is also important to construct a pharmacological audit trail linking molecular biomarkers and pharmacokinetic and pharmacodynamic parameters to tumor response end points. (page 4, lines 8-14, of final office action).

The clinical trials referred to by the Examiner are for determining efficacy and safety, which is beyond what is necessary to satisfy the enablement requirement of 35 USC §112, first paragraph. An applicant is not required to test the claimed compounds in their final use (rigorous planned and executed clinical trials..." per the Examiner) to satisfy the enablement requirement of 35 USC §112, first paragraph. As stated in *In re Brana*, 51 F.3d 1560, 34 USPQ2d 1436, 1442, (Fed. Cir. 1995) with respect to the utility requirement,

> FDA approval, however, is not a prerequisite for finding a compound useful within the meaning of the patent laws. *Scott*, 34 F.3d 1058, 1063, 32 USPQ2d 1115, 1120. Usefulness in patent law, and in particular in the context of pharmaceutical inventions, necessarily includes the expectation of further research and development. .... to require Phase II testing in order to prove utility, the associated costs would prevent any companies from obtaining patent protection on the promising new invention, thereby eliminating an incentive to pursue, through research and development, potential cures in any crucial area such as the treatment of cancer.

Although directed to the issue of utility, this rationale translates to prescribing the disclosure necessary to satisfy the enablement requirement of 35 U.S.C. § 112, first paragraph.

As stated in *In re Anthony*, 414 F2d 1383, 162 USPQ 594, 604 (CCPA 1969), "Approval by the FDA, is not a prerequisite for the patenting of a new drug." As to the issue of safety, *In re Anthony* held,

> ...Congress has given the responsibility to the FDA, not the Patent Office, to determine in the first instance whether drugs are sufficiently safe for use that they can be introduced in the commercial market, under the conditions prescribed,

recommended or suggested in the proposed labeling thereof, as the majority of this court noted in *Hartop*, 135 USPQ at 426, 427.

There is no requirement that an applicant provide any working examples relating to the treatment of a disease to satisfy the statute. See, for example, In re Marzocchi, 439 F.2d 220, 169 U.S.P.Q. 367 (CCPA 1971), stating that how "an enabling teaching is set forth, either by use of illustrative examples or by broad terminology, is of no importance." The MPEP also agrees by stating that "compliance with the enablement requirement of 35 U.S.C. 112, first paragraph, does not turn on whether an example is disclosed." See MPEP § 2164.02.

Here, the specification provides more than it needs to, e.g., *in vitro* raf kinase assays (and IC_{50} data) and *in vivo* assays (see pages 33 and 34). In similar fashion, one of ordinary skill in the art by performing the same or similar tests, can, by routine experimentation, determine the activity levels of each of the claimed compounds in treating various cancers. This is absolutely routine in the field. Applicants also point to *Bundy*, supra, where the disclosure only established the basic pharmacology for the compounds, but where no examples were provided. The specification stated that the compounds of the invention possess activity similar to E-type prostaglandins. Nevertheless it was found that sufficient guidelines as to use were given in the disclosure. The court held that "what is necessary to satisfy the how-to-use requirement of section 112 is the disclosure of some activity coupled with knowledge as to the use of this activity."

The rejection is clearly deficient in general under controlling case law. The courts have placed the burden upon the PTO to provide evidence shedding doubt on the disclosure that the invention can be made and used as stated; see, e.g., *In re Marzocchi*, 439 F.2d 220, 169 U.S.P.Q. 367 (CCPA 1971) (holding that how an enablement teaching is set forth, either by use of illustrative examples or by broad terminology, is of no importance.) The disclosure must be taken as in compliance with the enablement requirement of the first paragraph of § 112 unless there is reason to doubt the objective truth of the statements contained therein. See *In re Marzocchi*, supra. No such evidence or reason for doubting Applicants' disclosure has been provided. Only general statements and conclusions are made.

In a proper analysis of claims for compliance with 35 USC §112, first paragraph, a specification disclosure which

> contains a teaching of the manner and process of making and using the invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented must be taken as in compliance with the enabling requirement of the first paragraph of § 112 unless there is reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support. (Emphasis added.) *In re Marzocchi*, supra.

"The PTO must have adequate support for its challenge to the credibility of applicant's statements of utility". (The quoted statement was made in the context of enablement, i.e., the how-to-use requirement of the first paragraph of section 112.) See also *In re Bundy*, 642 F.2d 430, 209 USPQ 48, (CCPA 1981). The only relevant concern of the Patent Office should be over the truth of assertions relating to enablement. The first paragraph of section 112 requires nothing more than objective enablement. See *In re Marzocchi, supra.* The Examiner has not provided support for establishing that one of ordinary skill would doubt the objective truth of the asserted utility, which is the subject of the method claims. The rejection therefore is improper under *In re Marzocchi*.

No evidence has been presented that any compounds of this invention, as inhibitors of raf kinase, would not be effective in treating the cancers identified. Only unsupported allegations and conclusions regarding the art of cancer treatment are provided to support the rejection. The "purpose of treating cancer with chemical compounds does not suggest an inherently unbelievable undertaking or involve implausible scientific principles." See *In re Brana*, supra. Furthermore, there is no indication that one of ordinary skill in the art would have questioned the effect of the drugs in view of the disclosure and the state of the art. See *Rasmusson v. Smithkline Beecham Co.*, 75 USPQ2d 1297 (CA FC 2005). Applicants here provided detailed disclosure of how to use the claimed compounds and also provided data in the form of examples demonstrating activity of the claimed compounds.

The PTO has failed to meet its burden of establishing that the disclosure does not enable one skilled in the art to make and use the compounds recited in the claims. No evidence has been presented which would demonstrate that the guidance provided by the specification is inadequate to enable the use of the claimed compounds without undue experimentation.

Here, the specification provides more than it needs to, e.g., *in vitro* raf kinase assays (and

IC_{50} data) and *in vivo* assays. In similar fashion, one of ordinary skill in the art by performing the same or similar tests, can, by routine experimentation, determine the activity levels of each of the claimed compounds in treating diseases mediated by raf kinase, such as various cancers. It is alleged that appellants have not identified any state of the art references that clearly establish correlation between the assays employed in the specification and clinical efficacy for the treatment of the claimed diseases. Such a showing is not necessary here. The specification provides an objectively enabling disclosure and there is no necessity for any data at all. In any event, the party in interest is a pharmaceutical manufacturer, which would only use assays that were reasonably correlated with efficacy to find new products.

Thus, appellants have provided more than adequate guidance to enable the claimed invention.

For the reasons discussed above, Appellants submit that all claims on aapeal meet the requirements of 35 U.S.C. § 112, first paragraph and reversal of this rejection is respectfully requested.

The Rejection Under 35 USC § 103

The broadest generic disclosure of U.S. Patent No. 6,080,763 (Regan) embraces many thousands of compounds. The group ABDGE of formula I of Reagan (col. 6) alone encompasses over 100 heterocycles and does include a substituted pyrazole. In addition, specific pyrazole compounds are disclosed by Regan in the examples and the claims. However, neither the broad generic disclosure, nor the intermediate sub–generic disclosures nor the narrow specific disclosures suggest any of the compounds of claims 1, 2, 4, 5, 6, 9, 10, 30, 31 or 40 or compositions of claim 24, so as to render these claims obvious.

The compounds of the claims on appeal herein have a unique feature wherein the "aryl or hetaryl" groups of B are substituted by the bridged cyclic group: -M-L^1. Of the thousands of compounds encompassed by the disclosure of Regan, this reference does not provide one single example of a compound with a bridged cyclic group on the substituent "R^5", (which corresponds to the moiety "B" within the claims of this application). There are 42 pyrazole compounds described in Table 1 of Regan (col. 35-36), 5 pyrazole compounds described in claim 4 and in column 19 and one described in Example 2. These compounds show either no substituents on R^5 or a halogen, alkyl, cyano, alkoxy or phenyl substituent on R^5. Contrary to the Examiner's

findings, there is no basis within the teachings of Regan for concluding these substituents are equivalent to each other let alone equivalent to a bridged cyclic group (-M-L^1). The exemplified compounds suggest the opposite in that most have halogen substituents on the group R^5 and only one has a phenyl group. Therefore, there is clearly no motivation to either replace the substituents that appear on the exemplified pyrazole compounds with a bridged cyclic group or add such a substituent to these compounds based on the exemplified compounds and any of the teachings within the Regan reference.

In addition, this analysis has been held not to be the law in *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992):

> We decline to extract from *Merck* the rule that the Solicitor appears to suggest – that regardless of how broad, a disclosure of a chemical genus renders obvious any species that happens to fall within it. ... In contrast, though Richter discloses the potentially infinite genus of "substituted ammonium salts" of dicamba, and lists several such salts, the salt claimed here is not specifically disclosed. Nor, as we have explained above, is the claimed salt sufficiently similar in structure to those specifically disclosed in Richter as to render it *prima facie* obvious. (21 U.S.P.Q. 2d at 1943)

The broad generic disclosure and the subgeneric disclosures of Regan, do include bridged cyclic substituents in the lists given for substituents on R^5. These are in the form of phenyloxy and phenylamino groups in the narrowest subgeneric disclosure, which appears on col 16, line 66-col 19, line 8. However, these generic and subgeneric disclosures of compounds include heterocyclic structures other than pyrazole and include thioureas as well as ureas. One skilled in the art would need to make more then one selection of variables to arrive at the compounds claimed herein and there is no direction to select the bridged cyclic structures for pyrazole urea compounds based on the generic and subgeneric disclosures or the exemplified compounds of Regan.

No evidence has been presented that any of the compounds claimed herein are sufficiently similar in structure to those specifically disclosed in U.S. Patent No. 6,080,763 so as to render them *prima facie* obvious. Applicants submit that compounds claimed herein can only be found within the generic disclosures of US 6,080,763 when this application is used as a guide. Selections must be made for the heterocycle as well for the variables X and R_5 of Regan to obtain any of the compounds claimed. No evidence of any motivation to make the necessary selections or modify the specific compounds disclosed in US 6,080,763 to arrive at any of the compounds

claimed herein has been identified.

The examiner has identified a particular pyrazole compound and finds it is obvious to modify the compound to arrive at the claimed compounds based on the argument that one skilled in the art needs only to make one change. This improper procedure in essence poses the question: where can I look in this reference to find some sort of suggestion to place a bridged cyclic structure on the pyrazole compound identified, wherein the proper question is where in the reference is there any motivation to change this pyrazole compound. The difference between these two questions is a very heavy dose of improper hindsight.

When the proper question is asked, the answer is that there are a very large number of possible changes to the pyrazole compound identified which are mentioned by Regan and these include a wide variety of substituents and a wide variety of locations on the molecule. Even if any are particularly motivated, it is clear that the one necessary to arrive at the subject claimed compound is not. Thus, the examiner's comments alleging clear motivation for the alleged one change are incorrect. Regan only mentions the possibility of a very large number of changes and at best discloses that one "could" make many changes but in no way points to any particular change which arrives at the compounds of interest.

Claim 40

Claim 40 identifies specific pyrazole urea compounds, all of which have only a bridged cyclic structure on the moiety "B." To arrive at these compounds from those exemplified by Regan et al., it would be necessary to replace any substituents which appear on group R^5 with the specific bridged structures illustrated by each compound. There clearly is no direction from Regan to make such specific substitutions.

Method Claims

US 6,080,763 discloses that the compounds described therein are "useful for treating diseases and pathological conditions involving inflammation such as chronic inflammatory disease." These compounds are said to be inhibitors of inflammatory cytokines but there is no hint or suggestion any of the compounds are useful in treating raf mediated diseases. Furthermore, there is no hint or suggestion that the solid cancers and others described in claims 26-29 can be treated with the compounds of Formula I. Therefore, the methods of

claims 15, 16 18-23, 26-29 and 38 are clearly unobvious in view of this reference. In addition, all of these method claims are also non-obvious on the same basis as the compound claims, as explained above.

(IX) Conclusion

For the reasons stated above, Appellants respectfully submit the subject matter of the claims on appeal are novel and unobvious over the cited reference and the specification and claims satisfy the requirements of 35 U.S.C. §112, first and second paragraph. Therefore, Appellants respectfully request the outstanding rejections be reversed.

The Commissioner is hereby authorized to charge any fees associated with this response or credit any overpayment to Deposit Account No. 13-3402

Respectfully submitted,

Richard J. Traverso, Reg. No. 30,595
Attorney/Agent for Applicants

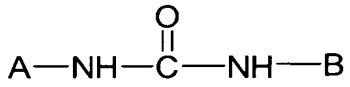
MILLEN, WHITE, ZELANO &
BRANIGAN, P.C.
Arlington Courthouse Plaza 1, Suite 1400
2200 Clarendon Boulevard
Arlington, Virginia 22201
Telephone: (703) 243-6333
Facsimile: (703) 243-6410

Attorney Docket No.: **BAYER-0009-C01**

Date: **March 13, 2006**

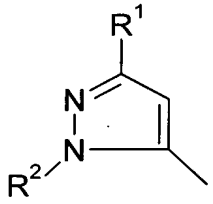
(viii) Claims Appendix

1. A compound of formula I or a pharmaceutically acceptable salt thereof



I

wherein A is



,

wherein R^1 is C_3-C_{10} alkyl, C_3-C_{10} cycloalkyl, up to per-halosubstituted C_1-C_{10} alkyl or up to per-halosubstituted C_3-C_{10} cycloalkyl;

B is an up to tricyclic, aryl or heteroaryl moiety of up to 30 carbon atoms with at least one 5- or 6-member aromatic structure containing 0–4 members of the group consisting of nitrogen, oxygen and sulfur, substituted by -M-L^1 and optionally substituted by one or more substituents independently selected from the group consisting of halogen, up to per-halosubstitution, and X_n,

wherein n is 0–2 and each X is independently selected from the group consisting of -CN, -CO_2R^5, -$C(O)NR^5R^{5'}$, -$C(O)R^5$, -NO_2, -OR^5, -SR^5, -$NR^5R^{5'}$, -$NR^5C(O)OR^{5'}$, -$R^5C(O)R^{5'}$, C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_1-C_{10} alkoxy, C_3-C_{10} cycloalkyl, C_6-C_{14} aryl, C_7-C_{24} alkaryl, C_3-C_{13} heteroaryl, C_4-C_{23} alkheteroaryl, substituted C_1-C_{10} alkyl, substituted C_2-C_{10} alkenyl, substituted C_1-C_{10} alkoxyl, substituted C_3-C_{10} cycloalkyl, up to per-halosubstituted C_6-C_{14} aryl, up to per-halosubstituted C_3-C_{13} heteroaryl, substituted C_4-C_{23} alkheteroaryl and -M-L^1;

where X is a substituted group, it is substituted by one or more substituents independently selected from the group consisting of -CN, -CO_2R^5, -$C(O)R^5$, -$C(O)NR^5R^{5'}$, -OR^5, -SR^5, -$NR^5R^{5'}$, -NO_2, -$NR^5C(O)R^{5'}$, -$NR^5C(O)OR^{5'}$ and halogen up to per-halosubstitution;

wherein R^5 and $R^{5'}$ are independently selected from H, C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_3-C_{10} cycloalkyl, C_6-C_{14} aryl, C_3-C_{13} heteroaryl, C_7-C_{24} alkaryl, C_4-C_{23} alkheteroaryl, up to per-halosubstituted C_1-C_{10} alkyl, up to perhalosubstituted C_2-C_{10} alkenyl, up to per-

halosubstituted C_3-C_{10} cycloalkyl, up to per-halosubstituted C_6-C_{14} aryl and up to per-halosubstituted C_3-C_{13} heteroaryl,

wherein M is -O-, -S-, -N(R^5)-, -(CH_2)-$_m$, -C(O)-, -CH(OH)-, -(CH_2)$_m$O-, -NR^5C(O)-, -C(O)NR^5, -(CH_2)$_m$S-, -(CH_2)$_m$N(R^5)-, -O(CH_2)$_m$-, -CHX^a-, -CX^a_2-, -S-(CH_2)$_m$- or -N(R^5)(CH_2)$_m$-, m = 1-3, and X^a is halogen; and

L^1 is a 5–10 member aromatic structure containing 0–2 members of the group consisting of nitrogen, oxygen and sulfur atoms, which is unsubstituted or substituted by halogen up to per-halosubstitution and optionally substituted by Z_{n1}, wherein n1 is 0 to 3 and each Z is independently -CN, -CO_2R^5, -C(O)N$R^5R^{5'}$, -C(O)NR^5, -NO_2, -OR^5, -SR^5, -N$R^5R^{5'}$, -NR^5C(O)O$R^{5'}$, -C(O)R^5, NR^5C(O)$R^{5'}$, C_1-C_{10} alkyl, C_3-C_{10} cycloalkyl, C_6-C_{14} aryl, C_3-C_{13} heteroaryl, C_7-C_{24} alkaryl, C_4-C_{23} alkheteroaryl, substituted C_1-C_{10} alkyl, substituted C_3-C_{10} cycloalkyl, substituted C_7-C_{24} alkaryl or substituted C_4-C_{23} alkheteroaryl;

wherein if Z is a substituted group, it is substituted by the one or more substituents independently selected from the group consisting of -CN, -CO_2R^5, -C(O)N$R^5R^{5'}$, -OR^5, -SR^5, -NO_2, -N$R^5R^{5'}$, -NR^5C(O)$R^{5'}$ and -NR^5C(O)O$R^{5'}$, and

wherein R^2 is C_6-C_{14} aryl, C_3-C_{14} heteroaryl, substituted C_6-C_{14} aryl or substituted C_3-C_{14} heteroaryl,

wherein if R^2 is a substituted group, it is substituted by one or more substituents independently selected from the group consisting of halogen, up to per-halosubstitution, and V_n,

wherein n = 0–3 and each V is independently selected from the group consisting of -CN, -CO_2R^5, -C(O)N$R^5R^{5'}$, -OR^5, -SR^5, -N$R^5R^{5'}$, -C(O)R^5, -OC(O)N$R^5R^{5'}$, -NR^5C(O)O$R^{5'}$, -SO_2R^5, -SOR^5, -NR^5C(O)$R^{5'}$, -NO_2, C_1-C_{10} alkyl, C_3-C_{10} cycloalkyl, C_6-C_{14} aryl, C_3-C_{13} heteroaryl, C_7-C_{24} alkaryl, C_4-C_{24} alkheteroaryl, substituted C_1-C_{10} alkyl, substituted C_3-C_{10} cycloalkyl, substituted C_6-C_{14} aryl, substituted C_3-C_{13} heteroaryl, substituted C_7-C_{24} alkaryl and substituted C_4-C_{24} alkheteroaryl,

where if V is a substituted group, it is substituted by one or more substituents independently selected from the group consisting of halogen, up to per-halosubstitution, -CN, -CO_2R^5, -C(O)R^5, -C(O)NR^5R^5, -N$R^5R^{5'}$, -OR^5, -SR^5, -NR^5C(O)$R^{5'}$, -NR^5C(O)O$R^{5'}$ and -NO_2;

wherein R^5 and $R^{5'}$ are each independently as defined above.

2. A compound of claim 1, wherein R^2 is substituted or unsubstituted phenyl or pyridinyl, and the substituents for R^2 are selected from the group consisting of halogen, up to

per-halosubstitution and V_n, wherein n = 0–3, and each V is independently selected from the group consisting of substituted and unsubstituted C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, C_6-C_{10} aryl, -NO_2, -NH_2, -C(O)-C_{1-6} alkyl, -C(O)N-(C_{1-6} alkyl)$_2$, -C(O)NH-C_{1-6} alkyl, -O-C_{1-6} alkyl, -NHC(O)H, -NHC(O)OH, -N(C_{1-6} alkyl)C(O)-C_{1-6} alkyl, -N-(C_{1-6} alkyl)C(O)-C_{1-6} alkyl, -OC(O)NH C_{6-14} aryl, -NHC(O)-C_{1-6} alkyl, -NHC(O)O-C_{1-6} alkyl, -S(O)-C_{1-6} alkyl and -SO_2-C_{1-6} alkyl,

wherein if V is a substituted group, it is substituted by one or more halogen, up to per-halosubstitution.

4. A compound of claim 1, wherein

M is selected from the group consisting of -O-, -S-, -CH_2-, -SCH_2-, -CH_2S-, -CH(OH), -C(O)-, -CX^a_2, -CX^aH-, -CH_2O- and -OCH_2-, and X^a is halogen.

5. A compound of claim 4, wherein

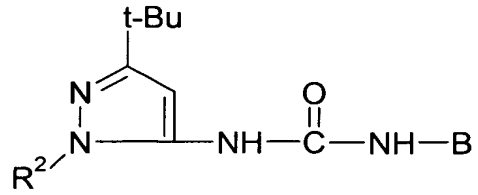
B is phenyl, naphthyl, a 5–6 membered monocyclic heteroaryl group having 1–4 hetero atoms independently selected from the group consisting of O, S and N or a 8–10 member bicyclic heteroaryl groups having 1–4 hetero atoms independently selected from the group consisting of O, S and N;

L^1 is selected from the group consisting of phenyl, pyridinyl, naphthyl, pyrimidinyl, quinolinyl, isoquinolinyl, imidazolinyl and benzothiazolyl, unsubstituted or substituted by halogen, up to per-halo substitution, and

Z and X are independently selected from the group consisting of -R^6, -OR^6 and -NHR^7, wherein R^6 is hydrogen, C_1-C_{10}-alkyl or C_3-C_{10}-cycloalkyl and R^7 is selected from the group consisting of hydrogen, C_3-C_{10}-alkyl, C_3-C_6-cycloalkyl and C_6-C_{10}-aryl, wherein R^6 and R^7 can be substituted by halogen ~~or~~ up to per-halosubstitution.

6. A compound of claim 1, wherein R^1 is t-butyl and R^2 is unsubstituted or substituted phenyl.

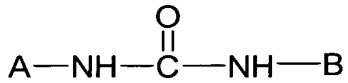
9. A compound of claim 1 of the formula



wherein B and R^2 are as defined in claim 1.

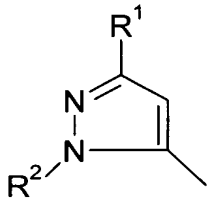
10. A compound of claim 9, wherein R^2 is selected from substituted and unsubstituted members of the group consisting of phenyl and pyridinyl, wherein if R^2 is a substituted group, it is substituted by one or more of the substituents selected from the group consisting of halogen and W_n, wherein n = 0–3, and W is selected from the group consisting of $-NO_2$, $-C_{1-3}$ alkyl, $-NH(O)CH_3$, $-CF_3$, $-OCH_3$, -F, -Cl, $-NH_2$, -OC(O)NH-up to per-halosubstituted phenyl, $-SO_2CH_3$, pyridinyl, phenyl, up to per-halosubstituted phenyl and C_1-C_6 alkyl substituted phenyl.

15. A method for the treatment of disease mediated by raf kinase, comprising administering an effective amount of a compound of formula I or a pharmaceutically acceptable salt thereof to a host in need thereof:



I

wherein A is



,

wherein R^1 is C_3-C_{10} alkyl, C_3-C_{10} cycloalkyl, up to per-halosubstituted C_1-C_{10} alkyl or up to per-halosubstituted C_3-C_{10} cycloalkyl;

B is a substituted or unsubstituted, up to tricyclic, aryl or heteroaryl moiety of up to 30 carbon atoms with at least one 5- or 6-member aromatic structure containing 0–4 members of the group consisting of nitrogen, oxygen and sulfur, substituted by $-M-L^1$ and optionally substituted by one or more substituents independently selected from the group consisting of halogen, up to per-halosubstitution, and X_n,

wherein n is 0–2 and each X is independently selected from the group consisting of -CN, CO_2R^5, $-C(O)NR^5R^{5'}$, $-C(O)R^5$, $-NO_2$, $-OR^5$, $-SR^5$, $-NR^5R^{5'}$, $-NR^5C(O)OR^{5'}$, $-NR^5C(O)R^{5'}$, C_1-C_{10} alkyl, C_{2-10}-alkenyl, C_{1-10}-alkoxy, C_3-C_{10} cycloalkyl, C_6-C_{14} aryl, C_7-C_{24} alkaryl, C_3-C_{13} heteroaryl, C_4-C_{23} alkheteroaryl, substituted C_1-C_{10} alkyl, substituted C_{2-10}-alkenyl, substituted C_{1-10}-alkoxy, substituted C_3-C_{10} cycloalkyl, up to per-halosubstituted C_6-C_{14} aryl, up to per-halosubstituted C_3-C_{13} heteroaryl, substituted C_4-C_{23} alkheteroaryl and M-L^1;

where X is a substituted group, it is substituted by one or more substituents independently selected from the group consisting of -CN, $-CO_2R^5$, $-C(O)R^5$, $-C(O)NR^5R^{5'}$, $-OR^5$, $-SR^5$, $-NR^5R^{5'}$, $-NO_2$, $-NR^5C(O)R^{5'}$, $-NR^5C(O)OR^{5'}$ and halogen up to per-halosubstitution;

wherein R^5 and $R^{5'}$ are independently selected from H, C_1-C_{10} alkyl, C_{2-10}-alkenyl, C_3-C_{10} cycloalkyl, C_6-C_{14} aryl, C_3-C_{13} heteroaryl, C_7-C_{24} alkaryl, C_4-C_{23} alkheteroaryl, up to per-halosubstituted C_1-C_{10} alkyl, up to per-halosubstituted C_{2-10}-alkenyl, up to per-halosubstituted C_3-C_{10} cycloalkyl, up to per-halosubstituted C_6-C_{14} aryl and up to per-halosubstituted C_3-C_{13} heteroaryl,

wherein M is -O-, -S-, $-N(R^5)$-, $-(CH_2)_m$-, -C(O)-, -CH(OH)-, $-(CH_2)_mO$-, $-(CH_2)_mS$-, $-(CH_2)_mN(R^5)$-, $-O(CH_2)_m$-, $-CHX^a$-, $-CX^a{}_2$-, $-S-(CH_2)_m$- or $-N(R^5)(CH_2)_m$-, m = 1–3, and X^a is halogen; and

L^1 is a 5- or 6-member aromatic structure containing 0–2 members of the group consisting of nitrogen, oxygen and sulfur atoms which is unsubstituted or substituted by halogen up to per-halosubstitution and optionally substituted by Z_{n1}, wherein n1 is 0 to 3 and each Z is independently -CN, $-C(O)R^5$, $-CO_2R^5$, $-C(O)NR^5R^{5'}$, $-C(O)NR^5$, $-NO_2$, $-OR^5$, $-SR^5$, $-NR^5R^{5'}$, $-NR^5C(O)OR^{5'}$, $-NR^5C(O)R^{5'}$, C_1-C_{10} alkyl, C_3-C_{10} cycloalkyl, C_6-C_{14} aryl, C_3-C_{13} heteroaryl, C_7-C_{24} alkaryl, C_4-C_{23} alkheteroaryl, substituted C_1-C_{10} alkyl, substituted C_3-C_{10} cycloalkyl, substituted C_7-C_{24} alkaryl or substituted C_4-C_{23} alkheteroaryl;

wherein if Z is a substituted group, it is substituted by the one or more substituents independently selected from the group consisting of -CN, $-CO_2R^5$, $-C(O)NR^5R^{5'}$, $-OR^5$, $-SR^5$, $-NO_2$, $-NR^5R^{5'}$, $-NR^5C(O)R^{5'}$ and $-NR^5C(O)OR^{5'}$, and

wherein R^2 is C_6-C_{14} aryl, C_3-C_{14} heteroaryl, substituted C_6-C_{14} aryl or substituted C_3-C_{14} heteroaryl,

wherein if R^2 is a substituted group, it is substituted by one or more substituents independently selected from the group consisting of halogen, up to per-halosubstitution, and V_n,

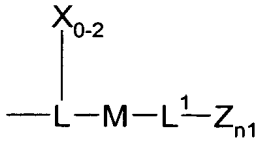
wherein n = 0–3 and each V is independently selected from the group consisting of -CN, $-CO_2R^5$, $-C(O)NR^5R^{5'}$, $-OR^5$, $-SR^5$, $-NR^5R^{5'}$, $-OC(O)NR^5R^{5'}$, $-NR^5C(O)OR^{5'}$, $-NR^5C(O)OR^{5'}$, $-SO_2R^5$, $-SOR^5$, $-NR^5C(O)R^{5'}$, $-NO_2$, C_1-C_{10} alkyl, C_3-C_{10} cycloalkyl, C_6-C_{14} aryl, C_3-C_{13} heteroaryl, C_7-C_{24} alkaryl, C_4-C_{24} alkheteroaryl, substituted C_1-C_{10} alkyl, substituted C_3-C_{10} cycloalkyl, substituted C_6-C_{14} aryl, substituted C_3-C_{13} heteroaryl, substituted C_7-C_{24} alkaryl and substituted C_4-C_{24} alkheteroaryl,

where V is a substituted group, it is substituted by one or more substituents independently selected from the group consisting of halogen, up to per-halosubstitution, -CN, $-CO_2R^5$, $-C(O)R^5$, $-C(O)NR^5R^5$, $-NR^5R^{5'}$, $-OR^5$, $-SR^5$, $-NR^5C(O)R^{5'}$, $-NR^5C(O)OR^{5'}$ and $-NO_2$,

wherein R^5 and $R^{5'}$ are each independently as defined above.

16. A method as in claim 15, wherein R^2 is selected from substituted or unsubstituted members of the group consisting of phenyl and pyridinyl, and the substituents for R^2 are selected from the group consisting of halogen, up to per-halosubstitution and V_n, wherein n = 0–3, and each V is independently selected from the group consisting of substituted and unsubstituted C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, C_6-C_{10} aryl, $-NO_2$, $-NH_2$, $-C(O)$-C_{1-6} alkyl, $-C(O)N$-(C_{1-6} alkyl)$_2$, $-C(O)NH$-C_{1-6} alkyl, $-O$-C_{1-6} alkyl, -NHC(O)H, -NHC(O)OH, $-N(C_{1-6}$ alkyl$)C(O)$-C_{1-6} alkyl, $-N$-(C_{1-6} alkyl$)C(O)$-C_{1-6} alkyl, $-NHC(O)$-C_{1-6}alkyl, $-NHC(O)O$-C_{1-6} alkyl, $-S(O)$-C_{1-6} alkyl and $-SO_2$-C_{1-6} alkyl, wherein if V is a substituted group, it is substituted by one or more halogen, up to per-halosubstitution.

18. A method of claim 15, wherein B is



wherein

M is selected from the group consisting of -O-, -S-, $-CH_2$-, $-SCH_2$-, $-CH_2S$-, -CH(OH)-, -C(O)-, $-CX^a_2$, $-CX^aH$-, $-CH_2O$- and $-OCH_2$-,

X^a is halogen,

L is six member aromatic structure containing 0–2 nitrogen, unsubstituted or substituted by halogen, up to per-halosubstitution;

L^1 is a mono- or bicyclic aromatic structure of 5–10 members with 3 to 10 carbon atoms and 0–2 members of the group consisting of N, O and S, unsubstituted or substituted by halogen up to per-halosubstitution,

X, Z, and n1 are as defined in claim 15.

19. A method as in claim 18, wherein

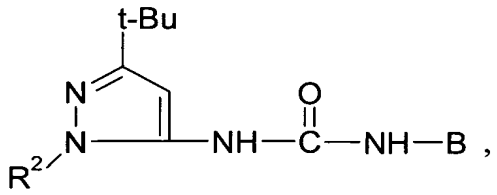
L is phenyl or pyridinyl, unsubstituted or substituted by halogen, up to per-halosubstitution,

L^1 is selected from the group consisting of phenyl, pyridinyl, naphthyl, pyrimidinyl, quinolinyl, isoquinolinyl, imidazolinyl and benzothiazolyl, substituted or unsubstituted by halogen, up to per-halo substitution, and

Z and X are independently selected from the group consisting of $-R^6$, $-OR^6$ and $-NHR^7$, wherein R^6 is hydrogen, C_1-C_{10}-alkyl or C_3-C_{10}-cycloalkyl and R^7 is selected from the group consisting of hydrogen, C_3-C_{10}-alkyl, C_3-C_6-cycloalkyl and C_6-C_{10}-aryl, wherein R^6 and R^7 can be substituted by halogen or up to per-halosubstitution.

20. A method as in claim 18, wherein L is phenyl, L^1 is phenyl or pyridinyl, M is -O-, -S- or $-CH_2-$, and X and Z are independently Cl, F, NO_2 or CF_3.

21. A method as in claim 15, which comprises administering a compound of the formula



wherein B and R^2 are as defined in claim 15.

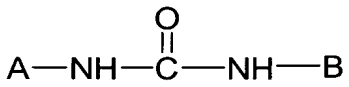
22. A method as in claim 21, wherein R^2 is selected from substituted and unsubstituted members of the group consisting of phenyl or pyridinyl, wherein if R^2 is a substituted group, it is substituted by one or more substituents selected from the group consisting of halogen and W_n, wherein n = 0–3, and W is selected from the group consisting of $-NO_2$, $-C_{1-3}$ alkyl, $-NH(O)CH_3$, $-CF_3$, $-OCH_3$, -F, -Cl, $-NH_2$, -OC(O)NH-up to per-

halosubstituted phenyl, $-SO_2CH_3$, pyridinyl, phenyl, up to per-halosubstituted phenyl and C_1-C_6 alkyl substituted phenyl.

23. A method as in claim 15, comprising administering an amount of compound of formula I effective to inhibit raf kinase.

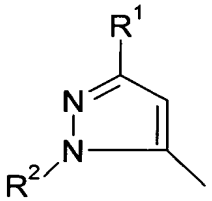
24. A pharmaceutical composition comprising an effective amount of a compound of claim 1 and a pharmaceutically acceptable carrier.

26. A method for treating a solid cancer, melanoma or adenoma, comprising administering an effective amount of a compound of formula I or a pharmaceutically acceptable salt thereof to a host in need thereof:



I

wherein A is



,

wherein R^1 is selected from the group consisting of C_3-C_{10} alkyl, C_3-C_{10} cycloalkyl, up to per-halosubstituted C_1-C_{10} alkyl and up to per-halosubstituted C_3-C_{10} cycloalkyl;

B is a substituted or unsubstituted, up to tricyclic, aryl or heteroaryl moiety of up to 30 carbon atoms with at least one 5- or 6-member aromatic structure containing 0–4 members of the group consisting of nitrogen, oxygen and sulfur, substituted by $-M-L^1$ and optionally substituted by one or more substituents independently selected from the group consisting of halogen, up to per-halosubstitution, and X_n,

wherein n is 0–2 and each X is independently selected from the group consisting of -CN, CO_2R^5, $-C(O)NR^5R^{5'}$, $-C(O)R^5$, $-NO_2$, $-OR^5$, $-SR^5$, $-NR^5R^{5'}$, $-NR^5C(O)OR^{5'}$, $-NR^5C(O)R^{5'}$, C_1-C_{10} alkyl, $C_{2\text{-}10}$-alkenyl, $C_{1\text{-}10}$-alkoxy, C_3-C_{10} cycloalkyl, C_6-C_{14} aryl, C_7-C_{24} alkaryl, C_3-C_{13} heteroaryl, C_4-C_{23} alkheteroaryl, substituted C_1-C_{10} alkyl, substituted $C_{2\text{-}10}$-alkenyl, substituted $C_{1\text{-}10}$-alkoxy, substituted C_3-C_{10} cycloalkyl, up to per-halosubstituted

C_6-C_{14} aryl, up to per-halosubstituted C_3-C_{13} heteroaryl substituted C_4-C_{23} alkheteroaryl and M-L^1;

where X is a substituted group, it is substituted by one or more substituents independently selected from the group consisting of -CN, -CO_2R^5, -$C(O)R^5$, -$C(O)NR^5R^{5'}$, -OR^5, -SR^5, -$NR^5R^{5'}$, -NO_2, -$NR^5C(O)R^{5'}$, -$NR^5C(O)OR^{5'}$ and halogen up to per-halosubstitution;

wherein R^5 and $R^{5'}$ are independently selected from H, C_1-C_{10} alkyl, $C_{2\text{-}10}$-alkenyl, C_3-C_{10} cycloalkyl, C_6-C_{14} aryl, C_3-C_{13} heteroaryl, C_7-C_{24} alkaryl, C_4-C_{23} alkheteroaryl, up to per-halosubstituted C_1-C_{10} alkyl, up to per-halosubstituted $C_{2\text{-}10}$-alkenyl, up to per-halosubstituted C_3-C_{10} cycloalkyl, up to per-halosubstituted C_6-C_{14} aryl and up to per-halosubstituted C_3-C_{13} heteroaryl,

wherein M is -O-, -S-, -$N(R^5)$-, -(CH_2)-$_m$, -C(O)-, -CH(OH)-, -$(CH_2)_mO$-, -$(CH_2)_mS$-, -$(CH_2)_mN(R^5)$-, -$O(CH_2)_m$-, -CHX^a-, -$CX^a{}_2$-, -S-$(CH_2)_m$- or -$N(R^5)(CH_2)_m$-, m = 1–3, and X^a is halogen; and

L^1 is a 5- or 6-member aromatic structure containing 0–2 members of the group consisting of nitrogen, oxygen and sulfur atoms which is unsubstituted or substituted by halogen up to per-halosubstitution and optionally substituted by Z_{n1}, wherein n1 is 0 to 3 and each Z is independently -CN, -$C(O)R^5$, -CO_2R^5, -$C(O)NR^5R^{5'}$, -$C(O)NR^5$, -NO_2, -OR^5, -SR^5, -$NR^5R^{5'}$, -$NR^5C(O)OR^{5'}$, -$NR^5C(O)R^{5'}$, C_1-C_{10} alkyl, C_3-C_{10} cycloalkyl, C_6-C_{14} aryl, C_3-C_{13} heteroaryl, C_7-C_{24} alkaryl, C_4-C_{23} alkheteroaryl, substituted C_1-C_{10} alkyl, substituted C_3-C_{10} cycloalkyl, substituted C_7-C_{24} alkaryl or substituted C_4-C_{23} alkheteroaryl;

wherein if Z is a substituted group, it is substituted by the one or more substituents independently selected from the group consisting of -CN, -CO_2R^5, -$C(O)NR^5R^{5'}$, -OR^5, -SR^5, -NO_2, -$NR^5R^{5'}$, -$NR^5C(O)R^{5'}$ and -$NR^5C(O)OR^{5'}$, and

wherein R^2 is C_6-C_{14} aryl, C_3-C_{14} heteroaryl, substituted C_6-C_{14} aryl or substituted C_3-C_{14} heteroaryl,

wherein if R^2 is a substituted group, it is substituted by one or more substituents independently selected from the group consisting of halogen, up to per-halosubstitution, and V_n,

wherein n = 0–3 and each V is independently selected from the group consisting of -CN, -CO_2R^5, -$C(O)NR^5R^{5'}$, -OR^5, -SR^5, -$NR^5R^{5'}$, -$OC(O)NR^5R^{5'}$, -$NR^5C(O)OR^{5'}$, -$NR^5C(O)OR^{5'}$, -SO_2R^5, -SOR^5, -$NR^5C(O)R^{5'}$, -NO_2, C_1-C_{10} alkyl, C_3-C_{10} cycloalkyl, C_6-C_{14} aryl, C_3-C_{13} heteroaryl, C_7-C_{24} alkaryl, C_4-C_{24} alkheteroaryl, substituted C_1-C_{10} alkyl,

substituted C_3-C_{10} cycloalkyl, substituted C_6-C_{14} aryl, substituted C_3-C_{13} heteroaryl, substituted C_7-C_{24} alkaryl and substituted C_4-C_{24} alkheteroaryl,

where V is a substituted group, it is substituted by one or more substituents independently selected from the group consisting of halogen, up to per-halosubstitution, -CN, $-CO_2R^5$, $-C(O)R^5$, $-C(O)NR^5R^5$, $-NR^5R^{5'}$, $-OR^5$, $-SR^5$, $-NR^5C(O)R^{5'}$, $-NR^5C(O)OR^{5'}$ and $-NO_2$,

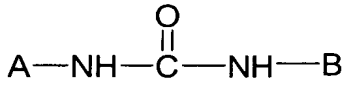
wherein R^5 and $R^{5'}$ are each independently as defined above.

27. A method as in claim 26, wherein the compound of formula I displays IC50s between 10nM and 10μM as determined by an in-vitro raf kinase assay.

28. A method according to claim 26, wherein the disease is a cancer dependent upon the raf protein signal transduction cascade and is treated by inhibiting raf kinase.

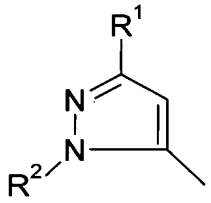
29. A method according to claim 26, wherein the solid cancer is a carcinoma of the lungs, pancreas, thyroid, bladder or colon.

30. A compound of formula I or a pharmaceutically acceptable salt thereof



I

wherein A is



,

wherein R^1 is C_3-C_{10} alkyl, C_3-C_{10} cycloalkyl, up to per-halosubstituted C_1-C_{10} alkyl or up to per-halosubstituted C_3-C_{10} cycloalkyl;

B is phenyl, pyridinyl, pyrimidinyl, pyrazinyl, pyridazinyl, naphthyl, quinolinyl, isoquinolinyl, phthalimidinyl, furyl, thienyl, pyrrolyl, imidazolyl, pyrazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, benzofuryl, benzothienyl, indolyl, benzopyrazolyl, benzoxazolyl, benzisoxazolyl, benzothiazolyl or benzisothiazolyl substituted by $-M-L^1$; and is optionally substituted by one or more substituents independently selected from the group consisting of halogen, up to per-halosubstitution, and X_n,

wherein n is 0–2 and each X is independently selected from the group consisting of -CN, $-CO_2R^5$, $-C(O)NR^5R^{5'}$, $-C(O)R^5$, $-NO_2$, $-OR^5$, $-SR^5$, $-NR^5R^{5'}$, $-NR^5C(O)OR^{5'}$, $-NR^5C(O)R^{5'}$, C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_1-C_{10} alkoxy, C_3-C_{10} cycloalkyl, C_6-C_{14} aryl, C_7-C_{24} alkaryl, C_3-C_{13} heteroaryl, C_4-C_{23} alkheteroaryl, substituted C_1-C_{10} alkyl, substituted C_2-C_{10} alkenyl, substituted C_1-C_{10} alkoxyl, substituted C_3-C_{10} cycloalkyl, up to per-halosubstituted C_6 -C_{14} aryl, up to per-halosubstituted C_3-C_{13} heteroaryl and substituted C_4-C_{23} alkheteroaryl and -M-L^1;

where X is a substituted group, it is substituted by one or more substituents independently selected from the group consisting of -CN, $-CO_2R^5$, $-C(O)R^5$, $-C(O)NR^5R^{5'}$, $-OR^5$, $-SR^5$, $-NR^5R^{5'}$, $-NO_2$, $-NR^5C(O)R^{5'}$, $-NR^5C(O)OR^{5'}$ and halogen up to per-halosubstitution;

wherein R^5 and $R^{5'}$ are independently selected from H, C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_3-C_{10} cycloalkyl, C_6-C_{14} aryl, C_3-C_{13} heteroaryl, C_7-C_{24} alkaryl, C_4-C_{23} alkheteroaryl, up to per-halosubstituted C_1-C_{10} alkyl, up to per-halosubstituted C_2-C_{10} alkenyl, up to per-halosubstituted C_3-C_{10} cycloalkyl, up to per-halosubstituted C_6-C_{14} aryl and up to per-halosubstituted C_3-C_{13} heteroaryl,

wherein M is -O-, -S-, $-N(R^5)$-, $-(CH_2)$-$_m$, -C(O)-, -CH(OH)-, $-(CH_2)_mO$-, $-NR^5C(O)$-, $-C(O)NR^5$, $-O(CH_2)_m$-, $-(CH_2)_mS$-, $-(CH_2)_mN(R^5)$-, $-CHX^a$-, $-CX^a_2$-, $-S-(CH_2)_m$- or $-N(R^5)(CH_2)_m$-, m = 1-3, and X^a is halogen; and

L^1 is phenyl, pyridinyl, pyrimidinyl, pyrazinyl, pyridazinyl, naphthyl, quinolinyl, isoquinolinyl, phthalimidinyl, furyl, thienyl, pyrrolyl, imidazolyl, pyrazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, benzofuryl, benzothienyl, indolyl, benzopyrazolyl, benzoxazolyl, benzisoxazolyl, benzothiazolyl or benzisothiazolyl, optionally substituted by halogen up to per-halosubstitution and optionally substituted by Z_{n1},

wherein n1 is 0 to 3 and each Z is independently -CN, $-CO_2R^5$, $-C(O)NR^5R^{5'}$, $-C(O)NR^5$, $-NO_2$, $-OR^5$, $-SR^5$, $-NR^5R^{5'}$, $-NR^5C(O)OR^{5'}$, $-C(O)R^5$, $NR^5C(O)R^{5'}$, C_1-C_{10} alkyl, C_3-C_{10} cycloalkyl, C_6-C_{14} aryl, C_3-C_{13} heteroaryl, C_7-C_{24} alkaryl, C_4-C_{23} alkheteroaryl, substituted C_1-C_{10} alkyl, substituted C_3-C_{10} cycloalkyl, substituted C_7-C_{24} alkaryl or substituted C_4-C_{23} alkheteroaryl;

wherein if Z is a substituted group, it is substituted by the one or more substituents independently selected from the group consisting of -CN, $-CO_2R^5$, $-C(O)NR^5R^{5'}$, $-OR^5$, $-SR^5$, $-NO_2$, $-NR^5R^{5'}$, $-NR^5C(O)R^{5'}$ and $-NR^5C(O)OR^{5'}$, and

wherein R^2 is optionally substituted phenyl, pyridinyl, pyrimidinyl, pyrazinyl, pyridazinyl, naphthyl, quinolinyl, isoquinolinyl, phthalimidinyl, furyl, thienyl, pyrrolyl,

imidazolyl, pyrazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, benzofuryl, benzothienyl, indolyl, benzopyrazolyl, benzoxazolyl, benzisoxazolyl, benzothiazolyl or benzisothiazolyl, wherein if R^2 is a substituted group, it is substituted by one or more substituents independently selected from the group consisting of halogen, up to per-halosubstitution, and V_n,

wherein n = 0–3 and each V is independently selected from the group consisting of -CN, $-CO_2R^5$, $-C(O)NR^5R^{5'}$, $-OR^5$, $-SR^5$, $-NR^5R^{5'}$, $-C(O)R^5$, $-OC(O)NR^5R^{5'}$, $-NR^5C(O)OR^{5'}$, $-SO_2R^5$, $-SOR^5$, $-NR^5C(O)R^{5'}$, $-NO_2$, C_1-C_{10} alkyl, C_3-C_{10} cycloalkyl, C_6-C_{14} aryl, C_3-C_{13} heteroaryl, C_7-C_{24} alkaryl, C_4-C_{24} alkheteroaryl, substituted C_1-C_{10} alkyl, substituted C_3-C_{10} cycloalkyl, substituted C_6-C_{14} aryl, substituted C_3-C_{13} heteroaryl, substituted C_7-C_{24} alkaryl and substituted C_4-C_{24} alkheteroaryl,

where if V is a substituted group, it is substituted by one or more substituents independently selected from the group consisting of halogen, up to per-halosubstitution, -CN, $-CO_2R^5$, $-C(O)R^5$, $-C(O)NR^5R^5$, $-NR^5R^{5'}$, $-OR^5$, $-SR^5$, $-NR^5C(O)R^{5'}$, $-NR^5C(O)OR^{5'}$ and $-NO_2$;

wherein R^5 and $R^{5'}$ are each independently as defined above.

31. A compound as in claim 30 wherein R^2 is phenyl, substituted phenyl, pyridinyl or substituted pyridinyl, L^1 is phenyl or pyridinyl, M is -O-, -S- or $-CH_2$, X and Z are independently Cl, F, CF_3, NO_2 or CN, and R^1 is t-butyl.

38. A method according to claim 29, wherein the solid cancer is a tumor.

40. A compound which is

- N-(1-(3-aminophenyl)-3-tert-butyl-5-pyrazolyl)-N'-(4-phenoxyphenyl) urea;
- N-(1-(3-actamidophenyl)-3-tert-butyl-5-pyrazolyl)-N'-(4-phenoxyphenyl) urea;
- N-(1-(3-nitrophenyl)-3-tert-butyl-5-pyrazolyl)-N'-(4-phenoxyphenyl)urea;
- N-(1-(phenyl)-3-tert-butyl-5-pyrazolyl)-N'-(4-(4-pyridinyl methyl)phenyl) urea;
- N-(1-(4 pyridinyl)-3-tert-butyl-5-pyrazolyl)-N'-(4-(4-pyridinyl methyl)phenyl) urea;

- N-(1-(2, 5 dichloro phenyl)-3-tert-butyl-5-pyrazolyl)-N'-(4-(4-pyridinyl methyl)phenyl) urea;
- N-(1-(4-fluoro phenyl)-3-tert-butyl-5-pyrazolyl)-N'-(4-(4-pyridinyl methyl)phenyl) urea;
- N-(1-(2-methyl phenyl)-3-tert-butyl-5-pyrazolyl)-N'-(4-(4-pyridinyl methyl)phenyl) urea;
- N-(1-(3 fluoro phenyl)-3-tert-butyl-5-pyrazolyl)-N'-(4-(4-pyridinyl methyl)phenyl) urea;
- N-(1-(4-methylsulfoxy phenyl)-3-tert-butyl-5-pyrazolyl)-N'-(4-(4-pyridinyl methyl)phenyl) urea;
- N-(1-(4-nitro phenyl) -3-tert-butyl-5-pyrazolyl)-N'-(4-(4-pyridinyl methyl)phenyl) urea;
- N-(1-(3-methoxy phenyl) -3-tert-butyl-5-pyrazolyl)-N'-(4-(4-pyridinyl methyl)phenyl) urea;
- N-(1-(3-amino phenyl) -3-tert-butyl-5-pyrazolyl)-N'-(4-(4-pyridinyl methyl)phenyl) urea;
- N-(1-(3-nitro phenyl) -3-tert-butyl-5-pyrazolyl)-N'-(4-(4-pyridinyl methyl)phenyl) urea;
- N-(1-(3-amino phenyl) -3-tert-butyl-5-pyrazolyl)-N'-(4-(4-pyridinyl thio)phenyl) urea.

(ix) EVIDENCE APPENDIX

None

(x) RELATED PROCEEDINGS APPENDIX

None